

# FLAGGING SYSTEMS FOR HEMATOLOGY ANALYZERS

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## Introduction

Clinical laboratories routinely use hematology instruments to perform so-called complete blood counts (CBCs) on patient specimens. About 25 different instruments are capable of performing blood counts that include differential leukocyte counts.<sup>(1)</sup> While the measurements performed by these instruments in general are quite accurate and precise, the measurements may vary from one brand of instrument to another.

Flagging is defined as “signaling or communicating a message with, or as if with, a flag.” In the hematology laboratory a flag is the signal to the operator that the analyzed *may have* a significant abnormality. Most of these automated instruments are programmed in a variety of ways to “flag” or otherwise identify specimens that may

a report is released from the laboratory.<sup>(5-8)</sup>

among the various instruments as to which abnormalities are flagged as well as the efficiency of the flagging procedures.

are quantitative flags, which are originally set by the manufacturer but which can be redefined by the user if desired. But it must be recognized that reference ranges may vary

<sup>(9)</sup> Therefore, quantitative flagging must take *not to*

for both qualitative and quantitative flags to its flagging menu.

To be useful, flagging should have a low false positive rate (e.g., < 10%) coupled

potentially abnormal blood specimens. However, it is recognized that there will be compromises between false negative and false positive flagging rates that are

which to strive, although not presently attainable.

The ultimate goal is to reduce the number of clinically non-contributory blood

third to one-half of these tedious reviews could be safely eliminated without adversely affecting patient care. Of course, in hematology and/or oncology services, it is most likely that most cases will have more frequent blood film reviews. As a bonus, the

shortened. But there may be a decrease in hospital revenues, which may pose a significant financial problem. Another potential problem may be the gradual loss of morphologic

become less proficient in this important function.

In our laboratories we began the development of a flagging system by interfacing<sup>(3)</sup> With the prototype

system in place, it was found that about one-third of the cases had no significant blood film review abnormalities and could be reported immediately. These instruments were later replaced by new analyzers that included acceptable flagging systems.<sup>(11)</sup> With the acceptance by the clinical staff over several years, the laboratories were able to reduce the rate of blood film reviews from 82% to less than 40%.

### **State of the Art for Flagging**

Performance of the most popular hematology instrumentation reveals reasonably good performance for quantitative abnormalities.<sup>(12-16)</sup> With time and experience, a laboratory may safely broaden the flagging limits beyond the narrow limits of the quantitative reference ranges. So, for example, as confidence builds that the instrument correctly counts neutrophils in the mildly and moderately abnormal ranges, the film review may be omitted if this is the only quantitative flag. Also, if a patient's blood film has been recently examined and the abnormality is still present, there is no need to repeat the examination.<sup>(8)</sup> As an example, patients undergoing cardiopulmonary bypass procedures frequently are thrombocytopenic and anemic in the immediate post-operative period. There is no need to re-examine blood films on consecutive specimens if the quantitative results are mildly abnormal and no marked changes have occurred.

Since the state-of-the-art hematology analyzers are quite acceptable insofar as quantitative measurements are concerned, there is little to be gained by a supplementary blood film examination. Thus a great deal of skilled technical effort can be devoted to other more useful endeavors. The following discussion will therefore concentrate on clinically meaningful *qualitative* abnormalities. In this case gender, age or even racial differences are of lesser importance. As a result the user has much less control over the qualitative flagging processes, which are proprietary for the most part.

The flagging performances for qualitative abnormalities have had false positive rates of up to 30% or more and false negative rates of up to 15%. It is difficult to compare the various instruments since many of the studies have been done with only one instrument. These data must be interpreted with caution since many times the case mix of the study specimens is not well defined or is variable from one study to the other; therefore, the rates of flagging misses are subject to variation due to the makeup of the study population rather than variation in instrument performance. Only a few studies have been published that compare several instruments using the same set of patient specimens.<sup>(17,18)</sup>

#### ***1) Flagging for Qualitative Red Cell Abnormalities***

Traditionally, red cell abnormalities have been categorized by the number, size and variability of the red cells, i.e., the red cell indices. Thus, microcytic, normocytic and macrocytic anemias as well as polycythemias have been quite adequately identified and categorized by hematology laboratories for many years. More recently, the determination of red cell anisocytosis has been measured by the so-called red cell distribution width (RDW) with some success, and additional categories of anemia have been developed.<sup>(19)</sup> In the recent past, there have been efforts to screen for hemoglobinopathies (in addition to thalassemias) that have shown promise of being useful in the discovery of certain

hemoglobinopathies. However, this capability has not yet been incorporated into all

Suggested flags for qualitative erythrocyte abnormalities include:  
Nucleated red cells in severe anemia, metastatic  
(22)

Poorly lysed red cells for hemoglobinopathies

.  
.  
(19)

While the quantitation of platelets has improved considerably in the recent past, Two additional platelet parameters have been proposed. The first, the mean platelet younger platelets are thought to be larger than normal. Thus an increase in the MPV has (23) often they are detected by analysis of the platelet histogram. platelet distribution width (PDW), is an of this measurement is still under investigation.

Studies have confirmed the accuracy and reliability of the total leukocyte count (12-16) monocyte differentiation has been problematic; this is probably of relatively minor (24) and variant [atypical] lymphocytosis), the instrument correlations with reference considered to be a shortcoming of the instruments while others take the stance that there especially surgeons and pediatricians, continue to rely on documenting these leukocyte bacterial).

.  
Variant lymphocytes for viral infections or lymphoproliferative disorders (22)  
.  
(25,26)

National Committee for Clinical Laboratory Standards (NCCLS) working group with the differential leukocyte counting standard.

#### **4) Unexpected Changes in Hematologic Parameters**

Finally, if there is a significant change (delta check) in any of the patient's quantitative or qualitative results even if they have occurred within the flagging limits, a blood film should be reviewed. For example, if the platelet count drops significantly within a relatively short period of time (hours or days), there is reason to investigate. Platelet clumping may account for the fall, but early disseminated intravascular coagulation might present in a similar way. Delta checking systems are not yet well developed nor are they yet widely available<sup>(29)</sup> but should be incorporated into the flagging procedures in the future.

#### **Quality Assurance Procedures for Flagging**

Since the flagging procedure by definition results in the examination of the blood film either to confirm or to rule out the presence of an abnormality, there is, in fact, an ongoing quality assurance procedure in place. A comprehensive discussion of quality assurance strategies for automated hematology analyzers has recently been published.<sup>(30)</sup> However, in order to ensure that no significant number of abnormalities are being missed, a representative sampling of non-flagged specimens should also be examined and records should be kept of such actions. This will also help to maintain the morphologic expertise of the laboratory staff. A recent chapter on blood film review outlines a practical yet comprehensive method for this procedure.<sup>(31)</sup>

#### **Future Directions**

Presently marketed hematology analyzers are capable of utilizing age and/or gender-specific flagging. While sophisticated laboratory information systems might include such a feature, as yet few such systems are in place. With continuing advances in the processing of data within the laboratory, a number of interfacing systems are being developed that may be able to help with the appropriate processing of the volume of data generated by the automated hematology analyzers. Some systems may be able to automatically flag specimens requiring additional study including, as appropriate, a blood film review by senior technologists and/or the medical director of the hematology laboratory. Some systems include the on-line evaluation of the data for validity.<sup>(32)</sup>

We have the opportunity to take advantage of the capabilities of automated hematology analyzers. If we can properly validate the hematology data and can flag specimens that need additional evaluation, patient care will be improved (by significantly shortening turnaround times), the efficiency of the laboratory staff will be enhanced (by eliminating unneeded or non-contributory blood film studies including differential counts) and finally the costs for laboratory studies will decrease. In these days of down-sizing and cost cutting, such innovations have become more difficult to investigate, develop and implement. Still, we should continue to strive to improve our laboratory services as well as to decrease costs.

In order to accomplish these worthwhile goals, laboratory and clinical professionals should continue to learn about the capabilities of the various analyzers and encourage harmonization of the various flagging systems, including the elimination of

International Council for Standards in Haematology is to develop standards in

## References

- CAP Surveys Manual. Section 2 - Hematology. College of American Pathologists, 1993, p. 817.
2. Hematology and Oncology IV. Year Book Medical Publishers, Chicago, 1986, p. 63.  
Koepke JA: Fitting the cell counter to the bed count. In PCJ Ward (ed): Routine Hematology. Philadelphia, 1993, p. 817.  
Houwen B, Koepke JA: The classic manual differential count and current practice. Philadelphia, 1990.  
Koepke JA, Dotson MA, Shifman MA, Boyarsky MW: A flagging system for automated blood counting systems. In B Roberts (ed): Standard Haematology Practice. London, 1991, p. 23.
6. Lewis SM, Rowan RM: Assessment of the need for blood film examination with automated blood counting systems. In B Roberts (ed): Standard Haematology Practice. Blackwell Scientific Publications. London, 1991, p. 34.
7. van Assendelft OW: Interpretation of the quantitative blood cell count. In JA Koepke (ed): Hematology Practice. Blackwell Scientific Publications. London, 1991, p. 6128.  
Brigden ML, Preece EV, Page NE: 'Diff/lf': A differential policy that works. Med J. 1990; 300: 3000.
11. Lacombe F, Cazaux N, Briaux A et al: Evaluation of the leukocyte differential. Am J Clin Pathol 99:72, 1993.
12. Hallowell R, O'Malley C, Hussein S, et al: An evaluation of the Sysmex NE-8000 hematology analyzer (Cobas Argos 5 Diff). Am J Clin Pathol 104:495, 1995.
13. Devices, November 1992, No. 11, ECRI. Plymouth Meeting, PA.
15. Lacombe F, Cazaux N, Briaux A et al: Evaluation of the leukocyte differential. Am J Clin Pathol 99:72, 1993.

17. Buttarello M, Gadotti M, Lorenz C, et al: Evaluation of four automated hematology analyzers. *Am J Clin Pathol* 97:345, 1992.
18. Bentley SA, Johnson A, Bishop CA: A parallel evaluation of four automated hematology analyzers. *Am J Clin Pathol* 100:626, 1993.
19. Bessman JD, Williams LJ, Gardner FH: Improved classification of anemias by MCV and RDW. *Am J Clin Pathol* 80:322, 1983.
20. Lamb A, Mallelian S, Freedman JJ: Detection of abnormal hemoglobinopathies by the Sysmex NE-8000 automated cell counter (Letter to the editor). *Br J Haematol* 88:567, 1991.
21. Honda SAA, Bhagavan VNV, Sugiyama CE, et al: Hemoglobinopathies detected by CBC analysis and HPLC Hemoglobin A<sub>1c</sub>. *Lab Med* 25:176, 1994.
22. Mayer K: Presence of abnormal cells. *Blood Cells* 11:25, 1985.
23. Bessman JD, Williams LJ, Gilmer PR: Mean platelet volume. The inverse relationship of platelet size and count in normal subjects and an artifact of other particles. *Am J Clin Pathol* 76:289, 1981.
24. Goossens W, Van Hove L, Verwilghen RL: Monocyte counting: Discrepancies obtained with different automated instruments. *J Clin Pathol* 44:224, 1991.
25. Mathy KA, Koepke JA: The clinical usefulness of segmented vs stab neutrophil criteria for differential leukocyte counts. *Am J Clin Pathol* 91:947, 1974.
26. Koepke JA: How should neutrophil reactions be measured? *Lab Hem* 1:87, 1995.
27. Dick FR: The lymphocytic differential count: Does it have potential? In JA Koepke (ed): *Differential Leukocyte Counting*. College of American Pathologists, Skokie, IL, 1978.
28. National Committee for Clinical Laboratory Standards. Reference leukocyte differential count (proportional) and evaluation of instrumental methods. Approved Standard NCCLS Document H20-A (ISBN 1-56-238). NCCLS, Villanova, PA 12:1, 1992.
29. Houwen B: Random errors in haematology tests: A process control approach. *Clin Lab Haem* 12(Suppl):157, 1990.
30. Bull BS: Quality assurance strategies. In JA Koepke (ed): *Practical Laboratory Hematology*. Churchill Livingstone, New York, 1991, pp. 3-29.
31. Shively JA: Interpretive aspects of hematology tests with a focus on the blood film. In SM Lewis, JA Koepke (eds): *Hematology Laboratory Management and Practice*. Butterworth-Heinemann, Oxford, 1995.
32. Davis GM: Autoverification of the peripheral blood count. *Lab Med* 25:528, 1994.